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The linear no-threshold model is less realistic than threshold or hormesis-based models: An evolutionary perspective

David Costantini[a,b,*], Benny Borremans[c,d,e]

[a] UMR 7221 CNRS/MNHN, Muséum National d'Histoire Naturelle, Sorbonne Universités, 7 rue Cuvier, 75005, Paris, France
[b] Behavioural Ecology & Ecophysiology Group, Department of Biology, University of Antwerp, Universiteitsplein 1, 2610, Wilrijk, Belgium
[c] Department of Ecology and Evolutionary Biology, University of California Los Angeles, 610 Charles E. Young Dr. South, Los Angeles, 90095, United States
[d] Evolutionary Ecology Group, Department of Biology, University of Antwerp, Universiteitsplein 1, 2610, Wilrijk, Belgium
[e] Interuniversity Institute for Biostatistics and Statistical Bioinformatics (I-BIOSTAT), Hasselt University, Agoralaan gebouw D, 3590, Diepenbeek, Belgium

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ABSTRACT

The linear no-threshold (LNT) risk model is the current human health risk assessment paradigm. This model states that adverse stochastic biological responses to high levels of a stressor can be used to estimate the response to low or moderate levels of that stressor. In recent years the validity of the LNT risk model has increasingly been questioned because of the recurring observation that an organism's response to high stressor doses differs from that to low doses. This raises important questions about the biological and evolutionary validity of the LNT model. In this review we reiterate that the LNT model as applied to stochastic biological effects of low and moderate stressor levels has less biological validity than threshold or, particularly, hormetic models. In so doing, we rely heavily on literature from disciplines like ecophysiology or evolutionary ecology showing how exposure to moderate amounts of stress can have severe impacts on phenotype and organism reproductive fitness. We present a mathematical model that illustrates and explores the hypothetical conditions that make a particular kind of hormesis (conditioning hormesis) ecologically and evolutionarily plausible.

1. Introduction

The origin of aerobic life is one of the most fascinating and elusive topics in biology. Certainly, one of the great leaps in the history of life on earth was the evolution of the capacity to use oxygen to generate energy [1]. As far as we know, oxygen expanded the metabolic and biochemical capacities of organisms, possibly contributing to the diversification of life [2]. Harnessing oxygen in aerobic metabolism to generate energy is not without hazards though, the most important being the generation of reactive oxygen species (ROS). If uncontrolled, these highly reactive by-products can wreak havoc, attacking all of the main building blocks from which bodies are made, including DNA, thus resulting in oxidative stress [3]. As a consequence, the need to evolve adequate defenses against the generation or accumulation of such damage arose in parallel with the use of oxygen by cells to generate energy [4]. Aside from oxygen metabolism, there have been numerous other potential sources of stress, such as changes in abiotic conditions.

Diversification of life and the spread of species into new and different environments meant that organisms faced new challenges, such as adaptation to new thermal regimes, fluctuations in water availability or salinity, variation in natural background ionizing radiation and in ultraviolet light. The nature of, and the interplay between, the costs and benefits involved in balancing offspring or energy generation against damage mitigation is a major area of research that cuts across many biological disciplines and levels of enquiry. What this research has taught us so far is that, while substantial molecular and higher-level damage can be detrimental for the organism, exposure to tiny amounts of such damage or to mild doses of environmental stressors (e.g., heat stress, ROS, radiation) may be essential for the organism [5–18].

In this review, we discuss current evolutionary thinking on the costs and benefits of stress exposure with a special reference to ionizing radiation, but also relying on examples of other environmental stressors. Although these examples include endpoints spanning the molecular to the organism level, the main focus is on reproductive fitness (or output) because to be successful in evolutionary terms an organism must pass its genes to the next generations, without mutations detrimental for fitness. To further explore these concepts, we present a novel mathematical model that explores and tests the hypothetical conditions that make a particular kind of hormesis (conditioning hormesis) ecologically and evolutionarily plausible.

* Corresponding author. UMR 7221 CNRS/MNHN, Muséum National d'Histoire Naturelle, Sorbonne Universités, 7 rue Cuvier, 75005, Paris, France.
E-mail address: david.costantini@mnhn.fr (D. Costantini).

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2. Dose–response models in toxicology and stress physiology

Axioms such as 'forewarned is forearmed' and 'that which harms often teaches' are cemented into our society, but not necessarily into our science. It is often assumed for an individual that the health or reproductive fitness declines (or e.g., cancer risk increases) as an LNT function of the dose of the stressor (e.g., chemical toxicant, abiotic stressor). This LNT decline which differs for different individuals is assumed to impact the risk of a given stochastic health effect (e.g., cancer), which is also characterized by an LNT model and can be justified on the basis of a Poisson distribution of cancer cases when there is a linear decline in health fitness.

The LNT model for characterizing the risk (or related endpoint such as relative risk) of a specific health effect has traditionally been a leading concept in several core disciplines (e.g., toxicology, radiation biology), but in recent years its validity has increasingly been questioned because it failed to accurately predict organism responses and outcomes (stochastic) related to low-dose stressor exposure [19–23]. The main reason for this is that knowledge about an individual's response to high doses has proven insufficient to predict its response to low doses, which raises important questions about the validity in evolutionary biology of the LNT risk model as it is currently used [e.g. [14,24,25]].

This research along with other research in this Special Issue and prior published work [e.g. [14]] shows that the LNT model is in most cases considered not biologically realistic. According to the threshold model, there is no significant effect (e.g., cancer induction) until the dose reaches a given threshold value (termed the 'No Observed Adverse Effect Level' in the toxicological literature), above which reproductive or other fitness traits decline (or physiological stress level increases) linearly or non-linearly with dose. Often, the dose-response relationship is biphasic, with low doses eliciting a stimulatory or beneficial organism response and high doses causing inhibition or toxicity, respectively. This form of biphasic dose-response is characteristic of hormesis [e.g. [5,19]].

In the following paragraphs, we review the findings of a number of ecological and evolutionary studies that show how the LNT model is less accurate than threshold and hormetic models, and present a hypothetical mathematical model that explores the conditions that make a particular kind of hormesis [termed "preconditioning hormesis" by Ref. [26]] evolutionary plausible.

3. Is the LNT model evolutionarily realistic and compatible with the need of DNA integrity maintenance?

DNA is the repository of genetic information in each organism. Its integrity and stability are both essential to life. DNA is also not inert because it is open to damage when an organism is being exposed to an environmental stressor. The premise of the LNT model is that the impact of some forms of environmental stressors, be it ionizing radiation or heat stress, on a biological endpoint, like DNA damage and consequent mutation frequency and cancer incidence, is directly proportional to the dose. Implicit in the assumptions of the LNT model is that an observable detrimental biological effect becomes evident when the magnitude of a given environmental stressor an organism is exposed to increases relative to a control situation (e.g., no radiation, no heat stress) and that the frequency of such a biological effect increases linearly with the dose. The assumptions justifying the LNT model are irreconcilable with current evolutionary theory for several reasons.

First, life on earth appeared and evolved in highly stressful environments where, for example, levels of ionizing radiation were much higher than background radiation levels today [27]. Thus, selection favoured evolution of numerous adaptive molecular mechanisms to deal with constant exposure to natural background radiation and other stressful conditions that organisms retain at present, such as those repairing damage to DNA. Consequently, any detrimental effects on reproductive or other fitness traits would be expected to be evident only above certain stress levels.

Second, all life on earth is exposed to background radiation with highly variable absorbed doses ranging from 0.01 to 260 mGy y^{-1} in humans [28,29]. Epidemiological and physiological studies did not find consistent differences in endpoints like DNA damage, cancer markers or chromosome aberrations between people living in areas with high naturally occurring background radiation and those living in areas with low background radiation [e.g. [28,30–32]].

Third, if organisms have adapted to thrive in the presence of radiation, how would they react to a significant decrease in environmental radiation dose? Work on protozoans, bacteria and fruitflies (*Drosophila melanogaster*) has shown that exposure to lower-than-background radiation levels can result in negative effects on fitness-related traits, compared to individuals exposed to background radiation [e.g. [33–35]]. Experiments on the protozoan *Paramecium tetraurelia* and the cyanobacterium *Synechococcus lividus* showed that shielding against background radiation was detrimental and that radiation hormesis only occurred in a limited range of doses above background level and disappeared for doses higher than 50 mGy y^{-1} [35]. Follow-up experiments on other organisms have found similar deleterious effects for exposure to below-background radiation, including (1) decreased protection to mutational damage in *Saccharomyces cerevisiae* [36], (2) higher sensitivity to apoptosis and intracellular oxidative stress in *Cricetulus griseus* [37], (3) reduction of growth rate in *Mus musculus* L5178Y cells [38], and (4) changes in the concentration of antioxidant enzymes [39] and in the expression of genes regulating DNA repair and response to oxidative stress in *Shewanella oneidensis* and *Deinococcus radiodurans* [40,41]. Recent work has actually shown that organisms exposed to lower-than-background radiation experience this unusual environment as stressful, leading to upregulation of many genes involved in protection against oxidative stress and down-regulation of those regulating protection of DNA [42].

Fourth, the LNT model is not accurate or biologically meaningful in predicting the organism response to low doses of a given stressor because it ignores the mechanisms that govern the organism's physiological adaptive stress responses. Implicit in the LNT model is the assumption that organism responses are elicited passively by environmental stimuli. Contrary to this outdated view, the organism more often actively decodes the information content of a given environmental stimulus and orchestrates a response to it. These potential responses are wide-ranging, including genetic and epigenetic mechanisms and phenotypic plasticity that translate into the activation of protective mechanisms of molecular integrity or of systems of damage repair [6–8,11,14–18].

Exposure to chemical toxicants or other kinds of stressors can also result in selection of resistant phenotypes or genotypes [43–47]. Translocation of these resistant individuals in areas free of that particular toxicant can cause reduced survival and reproduction [e.g. [43,44,46]]. This indicates that organisms adapted to a specific stressor might have developed a need of it, as otherwise the costs of maintaining protective mechanisms against a particular stressor would be too high to sustain. This is further supported by studies on phenotypic plasticity, which is the ability of an organism to change its phenotype [e.g., via preconditioning and postconditioning hormesis, 26] in response to changes in the environment.

In rapidly changing environmental conditions, the contribution of plasticity has critical implications for individuals and the evolution of populations by allowing adaptive traits to be rapidly introduced within a single generation [48,49]. This is particularly important when exposure to stress occurs early in life when the conditioning of the physiological system (preconditional hormesis) prepares the organism to withstand stress later in life [e.g. [16–18,50]]. Conditioning of stress responses in early life may carry fitness benefits providing the stressor is then encountered in the adult environment, while there might be a cost of phenotypic adjustment if there is no subsequent exposure to that

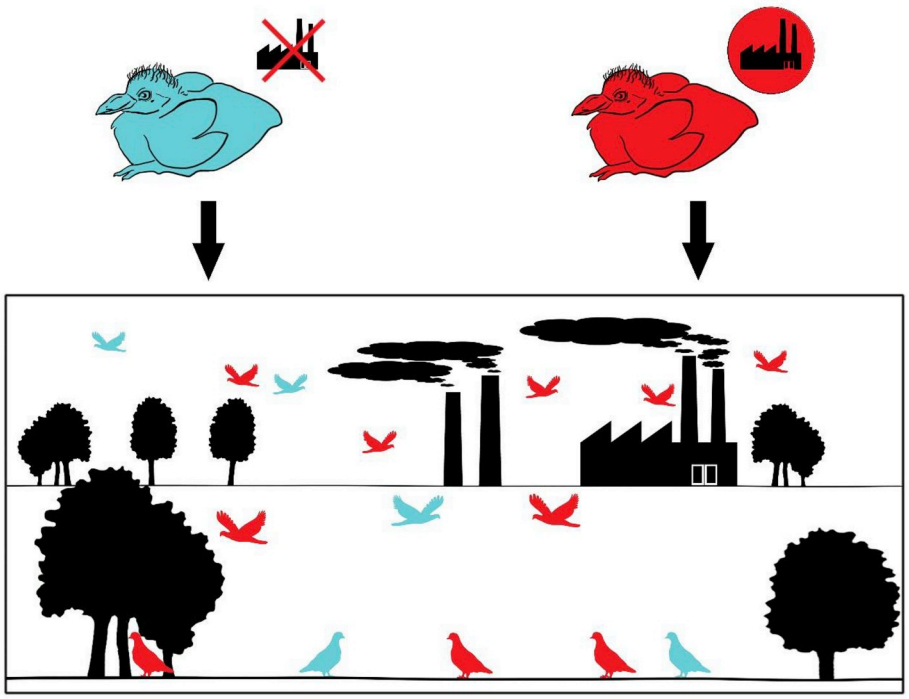

Fig. 1. Environmental conditions experienced while developing may have long-lasting consequences for the individual chances of surviving and reproducing. This illustration shows one hypothetical scenario about the consequences of developing in either a toxicant (or stress) free environment (blue nestling) or a mild polluted (or stressful) environment (red nestling). In adulthood, the population size of blue and red birds will be similar in low to mild stressful environments as long as there is not a cost due to mismatching between young and adult environmental conditions [e.g., 10]. In contrast, in environments where there is high pollution or stress red birds will outperform blue birds because of the early life conditioning hormesis of mechanisms to deal with stress. This hypothetical scenario would apply to species with low vagility, such as those that cannot rapidly disperse or migrate. Serena Costantini ©.

stressor in adulthood [10]. This may occur when the early life environment does not match the conditions experienced in adulthood. In other words, early life exposure to a mild dose of a chemical toxicant or of another environmental stressor (e.g., radiation, heat stress) might trigger phenotypic adjustments that would then translate in that individual being able to tolerate them better than when exposure to a high amount of the same stressor occurs in later life and, consequently, to flourish in challenging environments (Fig. 1). In the following paragraphs, we present further examples of experimental work supporting the idea that the key assumptions of the LNT model are generally wrong.

4. Evidence against the LNT model

4.1. Genetic evolution

Observational and experimental studies have shown that organisms can exhibit higher evolutionary rates when living under stressful conditions [e.g. [51,52]]. Earlier experiments on *Drosophila melanogaster* showed that genetic recombination (generation of a novel combination of genetic information that can be passed from the parents to the offspring) increases at development temperatures above or below normal culture temperatures, resulting in a U-shaped curve [53,54]. At near lethal temperature extremes, however, there is some evidence for a fall in recombination. Later experiments on *Drosophila melanogaster* [55,56] and other species [*Neurospora crassa* in Refs. [57,58]; *Coprinus lagopus* in Ref. [59]; *Caenorhabditis elegans* in Ref. [60]] found qualitatively similar results, implying that in mildly stressful environments, variability generated by recombination may increase. These results suggest potential for threshold or hormetic responses to facilitate evolutionary change.

A recent study on *Escherichia coli* showed that genetic innovations involving pre-existing DNA repair functions can play a predominant role in the acquisition of a phenotype resistant to increasing ionizing radiation [61]. Examples of evolutionary change in a short time can also be found in wild vertebrates. A recent study of Darwin's finches in the Galápagos Islands tells us that a complex trait, such as beak size, can evolve significantly in less than 1 year when the environment is stressful [62].

4.2. Stress resistance and survival

Some organism responses to radiation described in numerous species echo those resulting from some other types of stressors, which implies that mechanisms underlying threshold or hormetic responses are highly conserved across a wide range of species and stress agents (see below). For example, recent work on a bird species (zebra finch, *Taeniopygia guttata*) showed that exposure to relatively mild stress may have long-lasting positive consequences.

In two studies by Refs. [9,10], zebra finches encountering warmer-than-normal environments in adulthood showed increased resistance to molecular oxidative damage and long-term survival and resilience. However, this was observed only when they had been exposed to episodes of mild thermal stress before reaching sexual maturity. This work suggests that early-life exposure to mild stress may be beneficial when it matches (to some degree) the environmental conditions experienced later in life. When no heat stress was encountered in adulthood, however, survival was poorer in birds that experienced mild heat stress in early life than in those that did not, demonstrating a cost of preconditioning hormesis in the absence of a challenge in adulthood.

In another study on the zebra finch [63], showed that repeated exposure to the stressful conditions caused by unpredictable food availability (which induced no changes in body mass) was associated with an increase in lifespan. The birds responded to the unpredictable food supply by increasing baseline glucocorticoid stress hormones without any signs of habituation of this hormonal response to the treatment across time [63]. The increase of plasma concentration of glucocorticoids induced by the treatment was significant, but relatively mild, since the baseline glucocorticoid concentrations in the treated birds were substantially lower than the peak levels that occur during an acute stress response in this species [63]. These results led the authors to hypothesize that in a range of nutritional or other mild and unpredictable environmental stressors, hormetic responses via moderate stimulation of the Hypothalamic-Pituitary-Adrenal axis (which is responsible for the secretion of glucocorticoids) may represent an evolutionary conserved mechanism that promotes survival and reduces the

rate of ageing [63].

4.3. Variation among co-specific populations and species

Exposure to environmental stressors can contribute to shaping life diversity, and stress is something all living organisms experience. However, the intensity of environmental stressors varies in time and space, as does the coping capacity of populations and species. For example, while adverse health effects (e.g., cancer) do not show any appreciable increase in individuals living in areas with high natural background radiation, some aspects of cell resistance to stress appear to improve [28,30,64,65].

A recent meta-analysis of studies testing the effect of chronic low dose radiation on metrics of oxidative status (markers of oxidative damage, enzymatic and non-enzymatic antioxidants) found significant heterogeneity in effect size across species and tissues [66]. This conclusion suggests that there may be selection that acts on the capacity of organisms to cope with ionizing radiation (e.g., upregulation of DNA repair mechanisms, antioxidants). For example, while controlling for a number of potentially confounding variables, [67] showed that glutathione (an important intracellular antioxidant) levels increased, and lipid peroxidation and DNA damage decreased with increasing background radiation in some species of birds. These results might be due to genetic selection. For example, through directed evolution in the laboratory [61], generated populations of *Escherichia coli* exhibited a new phenotype characterized by extreme resistance to ionizing radiation due to increased DNA repair functions. Similarly, [68] suggested that hormetic mechanisms induced by environmental stressors might drive the evolution of genes regulating mechanisms that extend longevity. Alternatively, these results might be due to hormetic preconditioning [26] of the physiological system in order to tolerate higher levels of radiation. For example, experiments on genetically similar laboratory rodents found that individuals chronically exposed to doses of radiation slightly higher than background level lived longer than those exposed to background radiation [e.g. [69–71]].

Inter-species variation in tolerance of ionizing radiation might also be inferred from estimates of local abundance (i.e., number of individuals of a species living in a given area). The prediction is as follows: if external and internal exposure from radionuclides has no discernible impact on the health status of a species, abundance of that species in a highly radionuclide contaminated site would be expected to be similar to that in control sites. Although early work has shown negative effects on local abundance, number of eggs produced, immunity or body colourations in some bird species living in the highly contaminated Chernobyl Exclusion Zone [72], recent evidence suggests that populations of several mid-to large-sized carnivores, and of Eurasian boars, increased within the Chernobyl Exclusion Zone during the decades after the accident, and that mammal distributions across sites are uncorrelated with the severity of local radiation contamination [73,74]. These results suggest that the response of populations to radiation may vary across time, raising a difficulty in predicting responses in the long-term.

It is clear that it is not straightforward to predict whether in the long-term a species is going to flourish or perish in areas where there has been a small increase in background level of radiation. This conclusion does not seem surprising given that over the incipient stages of evolution of life the intensity of natural background radiation was much higher than it is now [27]. The conservative nature of DNA damage repair mechanisms in modern organisms suggests that these mechanisms evolved in the distant past and that living organisms retain the capability of efficiently repairing DNA damage from present radiation levels [27].

It is also important to consider that the biological effects of a given environmental stressor also depend on the co-exposure of the organism to additional stressors. For example, when experimentally exposed to high doses of gamma radiation (200–400 Gy), Caribbean fruit flies (*Anastrepha suspense*) suffered reduced survival, but when exposed to a combination of radiation and anoxic stress, survival of females was unaffected, while that of males was lower than controls yet significantly higher than males exposed only to irradiation. Exposure to a combination of irradiation and anoxic stress also improved resistance to oxidative stress and mating success of males. The strong tolerance of the marine tardigrade *Echiniscoides sigismundi* to radiation is due to molecular mechanisms that have evolved to allow survival of this organism to extreme dry environments [75]. These results further support the conclusion that evolution would not have been successful if the LNT model for stochastic biological effects were valid.

5. Modelling the conditions that make hormesis evolutionarily possible

Having presented substantial evidence that the LNT model is unlikely to be a good description of biological reality, we propose mathematical simulations to establish a better understanding of the evolutionary implications of hormesis. Relying on a number of realistic assumptions based on data available in the literature, mathematical simulations allow us to test relevant concepts without the need to perform experiments. Simulation models also allow us to formalize ideas, and have the added benefit of forcing us to define the most essential aspects of stress-response mechanisms. Although it would be possible to build a detailed model based upon empirical data on a well-studied model organism, we deliberately chose a general approach because the aim is to improve understanding at a conceptual level. Such models are a highly useful first step towards understanding the potential effects of environmental stressors on reproductive fitness [76].

Here, we present a simple hypothetical model that investigates the conditions under which mechanisms that allow preconditional hormesis [26] experienced during development can be expected to persist in a population. We focus on preconditional hormesis because much empirical research on stress physiology or longevity has provided convincing support for the biological relevance of this kind of hormesis and its applicability to many kinds of environmental stressors [e.g., 9–10].

More specifically, we investigate (i) how the degree of stress predictability during early and late life stages (stress (mis)match) is expected to affect the reproductive fitness of individuals in a population that have hormesis potential (HP), and (ii) how this reproductive fitness is affected by trade-offs between the benefits and costs of having HP. With use of the term HP we allow for genetic and epigenetic mechanisms driving hormetic responses to environmental stressors [77]. For example, [78] investigated the genetic variation of hormetic effects on lifespan induced by heat stress and the associated quantitative trait loci in various strains of *Caenorhabditis elegans*. Wild type CB4856 worms exposed to heat stress survived 18% longer than controls of the same strain. Using recombinant inbred lines (RILs) derived from a cross between wild types N2 and CB4856, [78] also found natural variation in stress-response hormesis in lifespan. More than one quarter (28%) of the RILs displayed a hormetic effect in lifespan induced by heat stress. Importantly, the ability to recover from heat-shock mapped to a significant quantitative trait locus (QTL) on chromosome II. The QTL was confirmed by infiltrating relatively small CB4856 regions into chromosome II of N2.

The model builds on realistic numbers of offspring that many bird and mammal species can generate at each reproductive event. It simulates a population of a generic species in which all individuals go through a young and an adult stage, after which they produce a certain number of offspring and die (i.e., no overlapping generations). We allow via our modelling for young stage individuals of a given species to experience three levels of stress (none, mild, severe), while during the adult stage they can experience two (none, severe).

While it would be possible to implement a range of stress levels experienced during adulthood, stress levels were intentionally limited to two in order not to make the final number of potential outcomes too

Table 1
Model conditions based on a set of simple rules. Each row describes a rule, the stage (young or adult) and stress condition (none, mild and severe for the young stage, and none or severe for the adult) at which it is applied, which individual class it applies to (Hormesis potential – HP and/or Hormesis negative – HN individuals), and the effect size by which it changes the number of offspring. The final number of offspring for each individual class at the end of a generation (young + adult stage) is calculated by summing each rule that was applicable for the conditions experienced during the young and adult stages.

Rule	Stage	Stress Level	Affects HP	Affects HN	Effect
1. Cost for being HP [Assumes that there is a cost for having hormesis potential, regardless of the experienced stress conditions]	Young	Any	X	–	−1
2. Cost of stress	Young	Mild	X	x	−1
3. Cost of stress	Young	Severe	X	x	−3
4. Cost of hormetic conditioning activation [Assumes that there is a cost for activating hormetic conditioning mechanisms]	Young	Mild	X	–	−0.5
5. Cost of stress	Adult	Severe	x	x	−2.5
6. Benefit of standard plasticity in case of mild stress during youth and severe stress during adulthood [Assumes that all individuals, regardless of whether they have hormetic conditioning potential, still develop a low level of resistance against future stress if they were exposed to mild stress in early life]	Adult	Severe	x	x	1.5
7. Benefit of hormetic conditioning in case of mild stress during youth	Adult	Severe	x	–	3.5
8. Benefit of standard plasticity in case of severe stress during youth and adulthood [Assumes that all individuals, regardless of whether they have hormetic conditioning potential, still develop a low level of resistance against future stress if they were exposed to severe stress in early life]	Adult	Severe	x	x	1

Table 2
Resulting total number of offspring for the different combinations of stress conditions, based on the standard set of rules described in Table 1.

Condition while young	Condition while adult	Final offspring number for HP individuals	Final offspring number for HN individuals
No stress	No stress	5	6
No stress	Severe stress	2.5	3.5
Mild stress	No stress	3.5	5
Mild stress	Severe stress	6	4
Severe stress	No stress	2	3
Severe stress	Severe stress	0.5	1.5

large, as this would make result interpretation unnecessarily difficult. For instance, the addition of a mild stress level during adulthood would generate a number of intermediate results between those generated by no or severe stress, but our interest lies in developing a conceptual understanding of the most extreme scenarios.

Exposure to a given stressor affects the number of offspring generated, but within the same species, individuals with HP are affected differently from those that are hormesis negative (HN, i.e., unable to generate an hormetic response): HP individuals can develop resistance against stress experienced during adulthood, but only if they were exposed to mild stress levels early in life. All model scenarios (which include a number of simulations) include a cost for being HP, which reflects the expected trade-off between investing in hormesis potential (self-maintenance) and in other traits (e.g., growth, reproduction). The model is based on a simple set of rules, described in Table 1, that determine how HP and HN offspring numbers are affected each generation, using a reference offspring number of 6 individuals (but note that the exact value is irrelevant and can be any number). For example, if individuals experience mild stress when young, and severe stress when adults, the number of offspring for HP individuals will be as follows: 6 (reference offspring number) −1 (rule 1: cost for being HP) −1 (cost of mild stress when young) −0.5 (cost for activating hormetic conditioning) −2.5 (cost of severe stress when adult) +1.5 (benefit of standard plasticity) +3.5 (benefit of hormetic conditioning), which adds up to a final offspring number of 6. Under the same conditions, the number of offspring for HN individuals will be: 6 (reference) −1 (cost of mild stress when young) −2.5 (cost of severe stress when adult) +1.5 (benefit of standard plasticity), adding up to a final offspring number of 4. In this situation, hormetic conditioning potential therefore yields a higher reproductive fitness. Table 2 shows the final offspring numbers for all possible stress combinations.

Each model run consists of 30 generations, where all individuals (starting with 50% HP and 50% HN) in each generation go through a young stage and an adult stage. At the start of a model run, one of three stress levels (none, mild, severe) is randomly chosen to be experienced by young individuals. Next, a stress level is generated for the following adult stage, according to a certain 'stress match probability' (SMP)

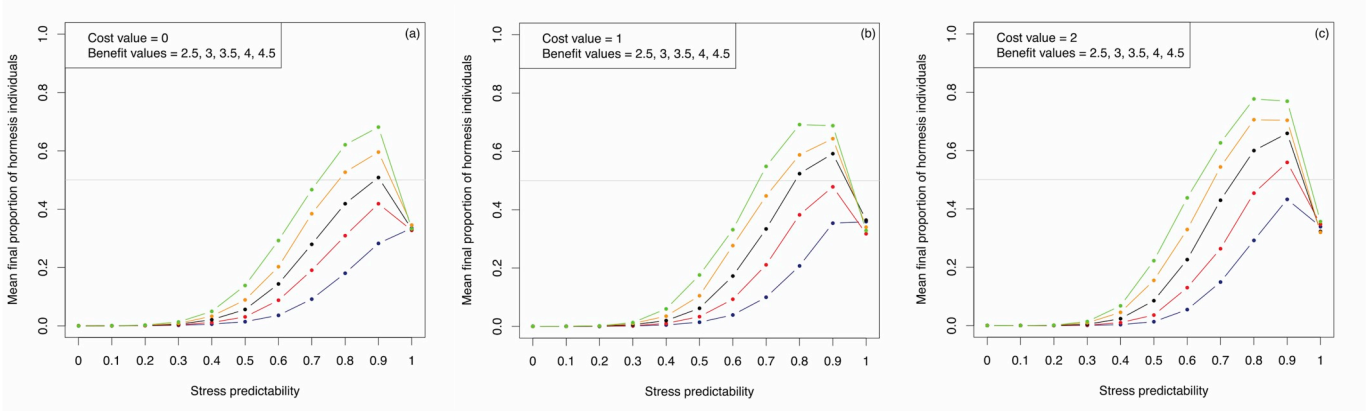

Fig. 2. Mean final proportion of HP individuals in the population for a range of stress match probabilities, under different combinations of mild stress cost values during youth and HP benefit values in the case of mild youth stress followed by adult stress. Benefit values shown in decreasing order from top (green line) to bottom (blue line). All other model values are the same as those shown in Table 1. The horizontal line indicates the transition where the reproductive fitness of HP is higher than that of HN.

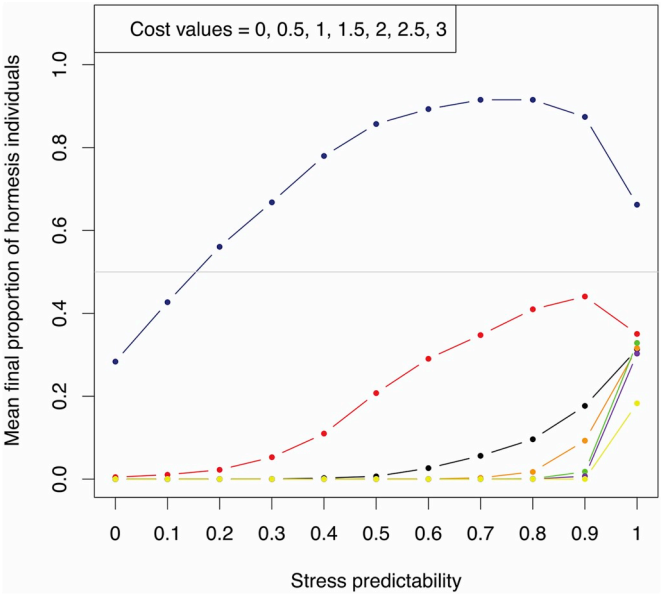

Fig. 3. Mean final proportion of HP individuals in the population for a range of stress match probabilities, and a range of cost values for hormesis potential, shown in increasing order from top (blue line) to bottom (yellow line). All other model values are the same as those shown in Table 1. The horizontal line indicates the transition where the reproductive fitness of HP is higher than that of HN.

value that is selected for that given model run. This value between 0 and 1 gives the probability of experiencing the same environmental conditions as those that were present during the young stage. For example, if the SMP is 1, the subsequent stress situation will always be the same as that during the previous stage. If the SMP is 0.7, there is a 70% chance that the subsequent situation will be the same, and a 30% chance that it changes. If the SMP is 0, the stress situation will always change. This means that for SMP values above 0.5 the stress level is more likely to be the same as the previous one, while for values below 0.5 the stress level is more likely to be different. The model goes through 30 generations, and the proportion of HP individuals in the population at the end of the 30^{th} generation is used as a proxy for HP reproductive fitness (i.e., evolutionary success). Thirty generations were chosen because this is sufficiently long to lose the influence of initial model stochasticity, and choosing a higher number of generations would not have affected the results (not shown).

A next step is to investigate which environmental stress conditions enable hormesis to persist in the population. We approach this question by analysing a number of model situations: (i) the effect of a range of stress match probabilities on HP reproductive fitness, (ii) the effect of the magnitude of the benefit offered by hormetic conditioning relative to the cost of mild stress during youth, (iii) the effect of the magnitude of the cost of being a HP individual. For each model situation, a set of cost and benefit values was chosen (based on the values shown in Table 1), and for each SMP value (all values from 0 to 1, in steps of 0.1) 1000 model runs were performed. This procedure was necessary because each model run is a random and stochastic outcome of the model. For each model run, the final proportion of HP individuals was retained, and the mean was calculated so that each model scenario had one single value of reproductive fitness.

The most important pattern that emerged from the simulations is that in most situations HP individuals can only survive in the population if stress conditions did not change too often. For all tested combinations of mild stress cost and hormetic conditioning benefit (Fig. 2), we observe a threshold behaviour, where HP individuals can only survive in the population at SMP values of 0.3 or higher, regardless of the magnitude of stress cost (Fig. 2a vs 2b vs 2c). In other words, if there is a low probability of stress conditions remaining the same, the benefit of conditioning never exceeds the cost of stress, even for high benefit values. It is also interesting to note that when stress occurrence is completely random (SMP = 0.5), there is always a proportion of HP individuals that can survive in the population (Fig. 2), except when the cost of being HP is high (Fig. 3). The cost of being HP has strong effects on HP reproductive fitness (Fig. 3): when there is no cost, HP individuals can always survive in the population and reproductively outperform HN individuals in most cases except when stress conditions are very likely to change (SMP < 0.2). As soon as there is a cost, however, HP reproductive fitness decreases rapidly, although there always seem to be some conditions of high stress predictability that allow a proportion of HP individuals to survive together with HN individuals.

6. Conclusions

Our review provides both empirical and theoretical evidence to conclude that the LNT model is not only invalid but also biologically unrealistic as compared to either threshold or hormetic models. It is beyond dispute that evolution has taken place in a number of extraordinarily stressful environments with simultaneous exposure to radiation, chemicals and abiotic factors (e.g., heat stress). This complex process has resulted in the appearance and positive selection of a number of stress response mechanisms (including mechanisms of damage repair), most of which are now highly conserved across species and underlie many of the threshold or hormetic responses to environmental stressors (including ionizing radiation) characterized to date. Our simulation models allowed us to define the most essential aspects of stress-response mechanisms underlying hormesis. It will be important to validate or refine our models using empirical data collected from well-defined experiments.

In conclusion, based on a large body of empirical data, in addition to theoretical assumptions, it is logical to conclude that if LNT were a biologically valid dose-response model, the evolution of life on Earth would not have been possible.

Conflicts of interest

Authors declare no conflict of interest.

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